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Identification of 2,3-diaryl-pyrazolo[1,5-*b*]pyridazines as potent and selective cyclooxygenase-2 inhibitors

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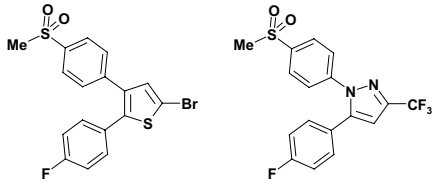
Abstract—GW406381 (**8**), currently undergoing clinical evaluation for the treatment of inflammatory pain is a member of a novel series of 2,3-diaryl-pyrazolo[1,5-*b*]pyridazine based cyclooxygenase-2 (COX-2) inhibitors, which have been shown to be highly potent and selective. Several examples of the series, in addition to possessing favourable pharmacokinetic profiles and analgesic activity in vivo, have also demonstrated relatively high brain penetration in the rat compared with the clinically available compounds, which may ultimately prove beneficial in the treatment of pain.

1. Introduction

Interest in the identification of highly selective inhibitors of cyclooxygenase-2 (COX-2) has been intense since the demonstration that early inhibitors such as DuP697 (**1**)[1] and SC 58125 (**2**)[2] produced analgesic efficacy in preclinical models that was not accompanied by the typical gastrointestinal toxicity produced by nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and indomethacin, and several groups have since reported potent and selective COX-2 inhibitors. Currently marketed inhibitors shown below (examples **3**–**6**) have now demonstrated clinical efficacy equivalent to NSAIDs in the treatment of inflammatory and musculoskeletal pain, but with a much improved gastric safety profile thus fulfilling the promise of this class (Figs. 1 and 2).

At the commencement of our work in this area all of the reported potent, selective COX-2 inhibitors possessed the typical core template associated with this class, that is, a 1,2-diaryl-substituted monocyclic heterocyclic ring. We were particularly interested in investigating structure–activity relationships of diaryl-substituted bicyclic heterocycles to establish whether these agents would demonstrate increased selectivity for the COX-2 isoform by more efficient occupation of the larger active site available in the COX-2 isoform relative to COX-1. Many of the bicyclic templates studied failed to give any significant activity. Two examples of active series are the imidazo[1,2-*a*]pyridines (e.g., **7**) and the pyrazolo[1,5-*b*]pyridazines (e.g., **8**). We initially chose to investigate a series of diaryl imidazo[1,2-*a*]pyridines (e.g., **7**),[3] many of which demonstrated high potency



1, DuP697 **2**, SC58125

Figure 1.

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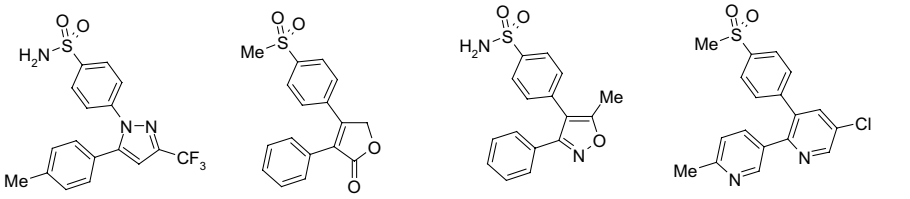


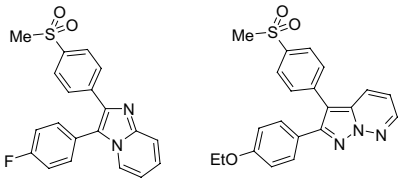
3, Celecoxib
COX-2 IC_{50} = 68nM
COX-1 IC_{50} = 1689nM

4, Rofecoxib
COX-2 IC_{50} = 32nM
COX-1 IC_{50} = >100,000nM

5, Valdecoxib
COX-2 IC_{50} = 183nM
COX-1 IC_{50} = >100,000nM

6, Etoricoxib
COX-2 IC_{50} = 347nM
COX-1 IC_{50} = >100,000nM

Figure 2.



7 **8**

Figure 3.

against the COX-2 enzyme. However, several members of the series surprisingly failed to show activity in a rat model of inflammatory pain, regardless of possessing adequate pharmacokinetic profiles. The lack of correlation between in vitro and in vivo activity for some members of the imidazo[1,2-*a*]pyridine template (**7**) could be argued to be a consequence of the relatively high log *D* values, and resulting unfavourable drug disposition for this series, and we have thus investigated a number of heterocyclic systems with reduced lipophilicity. This communication describes our investigation of the novel pyrazolo[1,5-*b*]pyridazine series (Fig. 3).

2. Chemistry

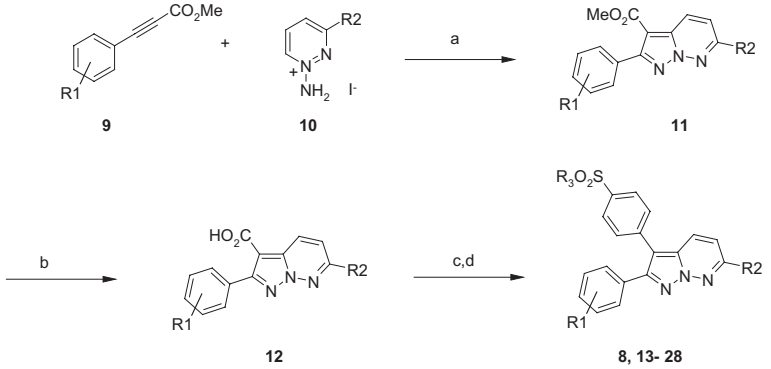
The key strategy for formation of the pyrazolo[1,5-*b*]pyridazine template was via a 1,3-dipolar cycloaddition as shown in Scheme 1.[4] Reaction of the acetylenic esters (**9**)[5] with the amino-pyridazinium salts (**10**)[6,7] in the presence of DBU generated the pyrazolo[1,5-*b*]pyridazine ring system (**11**). Saponification of the esters (**11**) furnished the corresponding acids (**12**). Bromo-decarboxylation by treatment with *N*-bromosuccinimide and sodium bicarbonate then provided the intermediate bromides, suitable for a final Suzuki coupling with the required boronic acid or boronate ester to rapidly generate the final targets with ready access to three points of diversity.

Alkoxy groups were introduced at R1 and R2 via demethylation of the corresponding methoxy substituted pyrazolopyridazine analogues (using either boron tribromide or pyridine hydrochloride) and subsequent alkylation of the resulting phenols (Fig. 4).

A sulfone residue at R2 (e.g., **28**) was formed by oxidation of the corresponding methylsulfide (e.g., **27**) using Oxone® in methanol and water at 25 °C (99% yield).

3. Results and discussion

The in vitro (recombinant human COX-1 and COX-2 enzymes[8]) and in vivo (Freund's Complete Adjuvant (FCA)[9]-induced arthritis model) potencies of the pyrazolo[1,5-*b*]pyridazines **8** and **13–31** are shown in Table 1, together with comparative data for known COX-2



9 **10** **11** **12** **8, 13- 28**

Scheme 1. Reagents and conditions: (a) DBU, CH_3CN, 25 °C (25–84%); (b) NaOH, EtOH, H_2O, reflux (72–99%); (c) NBS, $NaHCO_3$, DMF, 25 °C; (d) 4-(methanesulfonyl)phenyl boronic acid or dipinacol-4-(aminosulfonyl) benzene borate ester,[8] $Pd(PPh_3)_4$, Na_2CO_3, DME, H_2O, reflux (32–62% over steps c and d).

inhibitors. Full details of the profile of lead compounds in models of chronic pain is to be reported elsewhere.[8]

The compounds illustrated in Table 1 are highly potent COX-2 inhibitors and demonstrate excellent selectivity. Importantly, several of these compounds show a good correlation between in vitro potency and efficacy in the FCA model of inflammatory pain.

Substitution of the 2-phenyl ring (R1) of the pyrazolopyridazine with fluorine, alkyl and alkoxy groups is well tolerated. Although replacement of the sulfone moiety with a sulfonamide group (e.g., **18–20**) results in compounds with increased potency against COX-2, this is also accompanied by reduced selectivity against COX-1.

As is evident from Table 1, a range of substituents at the 6-position of the pyrazolo[1,5-*b*]pyridazine ring (R2) is well tolerated with high potency and selectivity for the COX-2 enzyme. This is particularly true when a phenyl sulfone group is present at the 3-position of the central pyrazolopyridazine template. As above replacement of the sulfone group by a sulfonamide (e.g., **23** and **24**) results in compounds which although still potent and selective COX-2 inhibitors, are less selective than the corresponding sulfones.

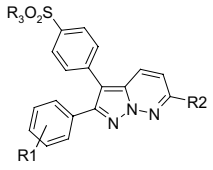


Figure 4.

Following administration of GW406381 (**8**) at a dose of 2 mg/kg to male rats as a 1 h iv infusion, GW406381 demonstrated low clearance (9 mL/min/kg) with a steady-state volume of distribution indicative of tissue distribution of 3.0 L/kg and a terminal half-life of 4.1 h. When administered by oral gavage at a dose of 5 mg/kg, using a clinically relevant formulation, oral bioavailability was approximately 80%.

There is an increasing body of evidence[10,11] to suggest that prostanoids play an important role in the central nervous system (CNS). Thus we have also determined the extent to which GW406381 and the current marketed compounds celecoxib and rofecoxib cross the blood–brain barrier in rats.[8] In view of the relatively high brain:blood concentration ratio of GW406381 (1.5:1) compared to rofecoxib (0.8:1) and celecoxib (0.1:1) we are investigating the potential of this compound in models of centrally mediated pain. The results of these studies will be reported elsewhere.[8]

In summary, we have rapidly prepared a novel series of pyrazolo[1,5-*b*]pyridazines as highly potent and selective COX-2 inhibitors, from which several compounds demonstrate good in vivo profiles.

Table 1. In vitro and in vivo properties of 2,3 diaryl-pyrazolopyridazines

Compound	R1	R2	R3	IC_{50} COX-2 (nM)[a]	IC_{50} COX-1 (nM)[b]	Selectivity[c]	FCA ED_{50} (mg/kg)[d]
8	4-OEt	H	Me	3	>84,200	>28,067	1.9
13	4-F	H	Me	39	>100,000	>2564	0.3
14	3-F	H	Me	34	58,300	1715	78% @ 10
15	H	H	Me	2	>100,000	>20,000	0.42
16	4-Me	H	Me	17	>19,100	>1107	23% @ 10
17	4-OMe	H	Me	<10	3880	>388	NT
18	4-F	H	NH_2	<10	24,100	>2410	0% @ 10
19	4-OEt	H	NH_2	0.44	3828	8700	0.5
20	4-OCF_3	H	NH_2	388	>100,000	>258	92% @ 10
21	4-F	Me	Me	24	>100,000	>4167	5.7
22	4-F	Et	Me	48	>100,000	>2083	40% @ 10
23	4-F	OMe	Me	51	>35,100	>688	10% @ 10
24	4-F	OMe	NH_2	26	2605	100	NT
25	4-H	Me	Me	<31	43,900	>1416	1% @ 10
26	4-Me	OMe	Me	50	>100,000	>2000	15% @ 10
27	4-OEt	SMe	NH_2	13	8630	664	NT
28	4-F	SO_2Me	Me	370	>100,000	>270	5
29	4-OEt	SO_2Me	NH_2	264	>100,000	>379	0% @ 10
30	4-F	OEt	Me	43	>100,000	>2326	11% @ 10
31	4-F	O*i*Pr	Me	57	>100,000	>1754	3
Celecoxib	—	—	—	68	1689	24.8	3.7
Rofecoxib	—	—	—	32	>100,000	>3125	1.0
Valdecoxib	—	—	—	183	>100,000	>546	3.2
Etoricoxib	—	—	—	347	>100,000	>288	1.0

[a] IC_{50} values for inhibition of PGE2 produced by arachidonic acid stimulated COS cells stably expressing human COX-2 as described in Ref. 8.
[b] IC_{50} values for inhibition of PGE2 produced by arachidonic acid stimulated COS cells stably expressing human COX-1 as described in Ref. 8.
[c] IC_{50} value for COX-1 divided by IC_{50} value against COX-2.
[d] Ref. 9, where ED_{50} values not determined % reversal at 10 mg/kg quoted.

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